

What is claimed is:

1. An antibody-based fusion protein with an enhanced circulating half-life, comprising at least a portion of an immunoglobulin (Ig) heavy chain having substantially reduced binding affinity for an Fc receptor, said portion of heavy chain being linked to a second non-Ig protein, said antibody-based fusion protein having a longer circulating half-life *in vivo* than an unlinked second non-Ig protein.
2. The antibody-based fusion protein of claim 1, wherein said portion of heavy chain comprises at least the CH2 domain of an ~~IgG2~~ or IgG4 constant region.
3. The antibody-based fusion protein of claim 1, wherein said portion of heavy chain comprises at least a portion of an IgG1 constant region having a mutation or a deletion at one or more amino acid selected from the group consisting of Leu<sub>234</sub>, Leu<sub>235</sub>, Gly<sub>236</sub>, Gly<sub>237</sub>, Asn<sub>297</sub>, and Pro<sub>331</sub>.
4. The antibody-based fusion protein of claim 1, wherein said portion of heavy chain comprises at least a portion of an IgG3 constant region having a mutation or a deletion at one or more amino acid selected from the group consisting of Leu<sub>281</sub>, Leu<sub>282</sub>, Gly<sub>283</sub>, Gly<sub>284</sub>, Asn<sub>344</sub>, and Pro<sub>378</sub>.
5. ~~The antibody-based fusion protein of claim 1, wherein said portion of heavy chain further has binding affinity for an immunoglobulin protection receptor.~~
6. The antibody-based fusion protein of claim 1, wherein said portion of heavy chain has substantially reduced binding affinity for a Fc receptor selected from the group consisting of FcγRI, FcγRII and FcγRIII.
7. The antibody-based fusion protein of claim 1, wherein said second non-Ig protein is selected from the group consisting of a cytokine, a ligand-binding protein, and a protein toxin.

8. The antibody-based fusion protein of claim 1, wherein said cytokine is selected from the group consisting of a tumor necrosis factor, an interleukin, and a lymphokine.
9. The antibody-based fusion protein of claim 8, wherein said tumor necrosis factor is tumor necrosis factor alpha.
10. The antibody-based fusion protein of claim 8, wherein said interleukin is interleukin-2.
11. The antibody-based fusion protein of claim 8, wherein said lymphokine is a lymphotoxin or a colony stimulating factor.
12. The antibody-based fusion protein of claim 11, wherein said colony stimulating factor is a granulocyte-macrophage colony stimulating factor.
13. The antibody-based fusion protein of claim 1, wherein said ligand-binding protein is selected from the group consisting of CD4, CTLA-4, TNF receptor, and an interleukin receptor.
14. A method of increasing the circulating half-life of an antibody-based fusion protein, comprising the step of linking at least a portion of an Ig heavy chain to a second non-Ig protein, said portion of heavy chain having substantially reduced binding affinity for an Fc receptor, thereby forming an antibody-based fusion protein having a longer circulating half-life *in vivo* than an unlinked second non-Ig protein.
15. The method of claim 14, wherein said portion of heavy chain comprises at least the CH2 domain of an IgG2 or IgG4 constant region.
16. A method of increasing the circulating half-life of an antibody-based fusion protein, comprising the steps of:
- (a) introducing a mutation or a deletion at one or more amino acid of an IgG1 constant region, said amino acid selected from the group consisting of Leu<sub>234</sub>, Leu<sub>235</sub>, Gly<sub>236</sub>, Gly<sub>237</sub>, Asn<sub>297</sub>, and Pro<sub>331</sub>, thereby producing an Ig

heavy chain having substantially reduced binding affinity for an Fc receptor; and

- (b) linking at least a portion of the heavy chain of step (a) to a second non-Ig protein,

thereby forming an antibody-based fusion protein having a longer circulating half-life *in vivo* than an unlinked second non-Ig protein.

- 17. A method of increasing the circulating half-life of an antibody-based fusion protein, comprising the steps of:

- (a) introducing a mutation or a deletion at one or more amino acid of an IgG3 constant region, said amino acid selected from the group consisting of Leu<sub>281</sub>, Leu<sub>282</sub>, Gly<sub>283</sub>, Gly<sub>284</sub>, Asn<sub>344</sub>, and Pro<sub>378</sub>, thereby producing an Ig heavy chain having substantially reduced binding affinity for an Fc receptor; and

- (b) linking at least a portion of the Ig heavy chain of step (a) to a second non-Ig protein,

thereby forming an antibody-based fusion protein having a longer circulating half-life *in vivo* than an unlinked second non-Ig protein.

- 18. The method of claim 14, 16 or 17, wherein said portion of heavy chain further has binding affinity for an immunoglobulin protection receptor.
- 19. The method of claim 14, 16 or 17, wherein said portion of heavy chain has substantially reduced binding affinity for a Fc receptor selected from the group consisting of FcγRI, FcγRII and FcγRIII.
- 20. The method of claim 14, 16 or 17, wherein said second non-Ig protein is selected from the group consisting of a cytokine, a ligand-binding protein, and a protein toxin.
- 21. The method of claim 14, 16 or 17, wherein said cytokine is selected from the group consisting of a tumor necrosis factor, an interleukin, and a lymphokine.

22. The method of claim 21, wherein said tumor necrosis factor is tumor necrosis factor alpha.
23. The method of claim 21, wherein said interleukin is interleukin-2.
24. The method of claim 21, wherein said lymphokine is a lymphotoxin or a colony stimulating factor.
25. The ~~antibody~~-based fusion protein of claim 24, wherein said colony stimulating factor is a ~~granulocyte-macrophage~~ colony stimulating factor.
26. The method of claim 14, 16 or 17, wherein said ligand-binding protein is selected from the group consisting of CD4, CTLA-4, TNF receptor, and an interleukin receptor.

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